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Acute severe Cushing's disease presenting as a hypercoagulable state

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ABSTRACT

Cushing's disease (CD) is the most common cause of endogenous cortisol excess. We discuss the case of a 60-year-old woman with recurrent venous thromboembolism, refractory hypokalemia, and lumbar vertebrae compression fractures with a rapidly progressive disease course. Ectopic hypercortisolism was suspected given the patient's age and rapid onset of disease. Investigations revealed cortisol excess from a pituitary microadenoma. This case demonstrates that CD can present with severe findings and highlights the increased risk of venous thromboembolism in hypercortisolism, especially in CD.

KEYWORDS Cortisol; Cushing's disease; fracture; hypercoagulability; thromboembolism

Cushing's disease (CD), the most common cause of endogenous hypercortisolism, is caused by excessive secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland.[1] Typical symptoms of hypercortisolism include proximal muscle weakness, increased supraclavicular, abdominal, and facial fat, purple striae, and round facies.[2] A severe acute presentation is typically seen in patients with ectopic ACTH syndromes. We present a case of severe acute hypercortisolism from Cushing's disease presenting with venous thromboembolism (VTE) posing a clinical diagnostic challenge.

CASE REPORT

A 60-year-old woman was admitted to the hospital with persistent dyspnea, fatigue, and anemia. She was recently diagnosed with type 2 diabetes mellitus, deep venous thrombosis, and pulmonary embolism requiring anticoagulation. On examination, she appeared cachectic with multiple ecchymoses on all extremities and a nonhealing ulcer on her right ankle. Of note, there was no evidence of moon facies, supraclavicular fat pads, or abdominal striae. Her body mass index was 17.34 kg/m^2 and her blood pressure was in the range of 143–162/79–105 mm Hg. Her serum potassium was 3.3 mEq/L and sodium was 147 mEq/L. A computed tomography (CT) scan of the abdomen revealed a retroperitoneal hematoma and L1, L2 vertebral compression fractures. Ecchymoses and a retroperitoneal hematoma were attributed to anticoagulation. Following discontinuation of anticoagulation, she developed another deep venous thrombosis in her left lower extremity. Workup for inherited or acquired disorders of coagulation was negative. Hypokalemia proved to be refractory to oral and intravenous replacement, going as low as 1.7 mEq/L. Her blood glucose also proved difficult to control, with varying insulin requirements. Her hemoglobin A1c was 9.4% (76 mmol/mol).

The refractory and profound hypokalemia, wide excursions in blood glucose, and vertebral compression fractures in the setting of a hypercoagulable state raised suspicion of hypercortisolism. Laboratory testing revealed elevated random cortisol, loss of circadian rhythm with elevated midnight cortisol, and failure of a low-dose dexamethasone suppression test (DST) *(Table 1)*. A high-dose DST showed a response with relative decline of cortisol and ACTH. No masses were seen on CT imaging of the chest, abdomen, and pelvis. No pituitary enlargement or intracranial masses were seen on magnetic resonance imaging (MRI). A corticotropin-releasing hormone stimulation test showed an immediate rise in ACTH and cortisol. Subsequently, inferior petrosal venous sinus sampling showed lateralization to the right, confirming a pituitary microadenoma as the source of excessive ACTH. A transsphenoidal hypophysectomy was planned. In

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Table 1. Biochemical evaluation of hypercortisolism

Variable	Result	Reference range
Cortisol		
Random (mcg/dL)	44	
8 AM (mcg/dL)	122	6.0–18.4
8 AM ACTH (pg/mL)	154	7.2–63.3
Midnight (mcg/dL)	121*	
Low dose DST: cortisol (mcg/dL)	112–151	
High-dose DST (overnight 8 mg)		
Cortisol (mcg/dL)	38	↓ >50%
ACTH (pg/mL)	67	
CRH stimulation test		
Cortisol (mcg/dL)	49 / – / 89**	
ACTH (pg/mL)	84 / 366 / 76**	

*Indicating loss of circadian rhythm.
**Baseline/after 10 min/after 25 min.
ACTH indicates adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test.

the midst of investigations, the patient developed another pulmonary embolism complicated by bacterial pneumonia, resulting in significant deterioration of her clinical status, and she unfortunately succumbed to the disease.

DISCUSSION

The most common etiology of hypercortisolism (or Cushing syndrome) is iatrogenic or exogenous administration of glucocorticoids. CD (ACTH-secreting pituitary adenoma) is the most common endogenous cause of hypercortisolism. CD is underreported and associated with increased mortality, particularly in the first year after diagnosis.[3] Common clinical features of CD are those of chronic hypercortisolism: obesity, round face, hirsutism, supraclavicular fat pads, purple striae, hypertension, and impaired glucose tolerance.[4] Acute severe symptoms of hypercortisolism are uncommon in CD and are typically noted in ectopic ACTH syndromes.[5] Our patient had an acute, severe, and rapidly progressing clinical presentation with multiple metabolic consequences in the absence of a typical clinical phenotype.

Thromboembolic events are relatively uncommon and often underrecognized manifestations of CD. The incidence of VTE in patients with hypercortisolism is 2.5 to 3.1 per 1000 person-years, compared to 0.3 per 1000 person-years in age- and gender-matched controls.[6–8] The hypercoagulable state in hypercortisolism is believed to be from glucocorticoid-induced increases in factor VIII, homocysteine, and von Willebrand factor levels, as well as a reduction in fibrinolytic activity.[9–11] Obesity, reduced mobility, older age, and systemic infections add to these patients' risk of developing a VTE.

Approximately 40% of patients with CD have no visible tumor on standard MRI of the brain,[12] as 90% to 95% of these tumors are microadenomas. Excessive ACTH production is followed by the loss of ACTH circadian rhythm, becoming independent of hypothalamic regulation and resistant to glucocorticoid feedback inhibition,[13] causing adrenal hyperplasia and subsequent loss of circadian rhythm in cortisol secretion as well.[14] The pituitary functions as if its threshold for glucocorticoid feedback inhibition is raised. Therefore, in most cases, there will be a positive response to high levels of glucocorticoids, defined by suppression of cortisol to <50% of the basal value. At other times, this response can be blunted[15] and these intermediate values are not helpful in distinguishing a pituitary and ectopic source of ACTH. Adequate cortisol suppression was observed with high-dose DST in our patient. An unremarkable pituitary MRI added to the clinical dilemma. Corticotropin-releasing hormone stimulation and bilateral inferior petrosal sinus sampling confirmed the diagnosis of pituitary CD.

The first line of treatment of CD is transsphenoidal surgery. Mifepristone can help block the effect of cortisol at glucocorticoid receptors. Medical therapy with cabergoline or pasireotide, pituitary irradiation, or bilateral adrenalectomy can be considered if pituitary surgery is unsuccessful or not possible. Currently, anticoagulation in Cushing's syndrome is recommended only postoperatively to reduce the risk of VTE. There is a lack of data regarding the benefit of preemptive anticoagulation in patients with hypercortisolism or CD to prevent VTE or its complications, and as such there is no recommendation for routine use of anticoagulants.

In conclusion, though typically an indolent disease, CD can present with atypical and severe findings. Clinical distinction is not always easy, and unremarkable imaging can add to the diagnostic dilemma. This case demonstrates the increased risk of VTE in hypercortisolism, especially in CD. Hypercortisolism should be considered in patients with unprovoked VTE, and a thorough investigation for additional signs and symptoms is warranted before the disease progresses.

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